IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Daniel G. Chain	Art Unit	: 1649
Serial No.	: 10/084,380	Examiner	: Gregory S. Emch
Filed	: February 28, 2002	Conf. No.	: 3496
Title	: **SPECIFIC ANTIBODIES TO AMYLOID BETA PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHODS OF USE THEREOF**		

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P.O. Box 1450
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DECLARATION OF NORMAN R. RELKIN, M.D., PH.D., UNDER 37 C.F.R. 1.132

Norman R. Relkin declares and states as follows:

1. I am a citizen of the United States and am more than twenty-one years of age.

2. I am an associate professor of Clinical Neurology and Neuroscience at Weill Cornell Medical College. I obtained a doctoral degree (Ph.D.) in Neuroscience as well as a medical doctorate (M.D.) in 1987. I joined the Cornell Medical College faculty in 1991. I am the founding director of the Weill Cornell Memory Disorders Program. I became Board Certified in Neurology in 1992. I am a practicing physician in the Memory Disorders subspecialty of Neurology and have recognized expertise relating to Alzheimer's disease (AD). I also am also the head of a research laboratory at Weill Cornell that carries out basic and translational studies relating to AD immunotherapy.

3. I have conducted research in the field of AD since 1993. Specifically, I have studied methods of improving prediction, diagnosis and treatment of AD and other forms of dementia. I am a co-inventor of U.S. patent application no. 11/910,721, published as US 20090075395 A1, and entitled, "Multiplexed Biomarkers for Monitoring the Alzheimer's Disease State of a Subject." I have participated in, designed and/or led more than a dozen AD clinical trials, including Phase 1 and 2 trials of Intravenous Immunoglobulin (IGIV) for treatment of mild to moderate AD. I designed and currently lead the NIH/Baxter co-sponsored Phase 3 pivotal study of IGIV for the treatment of mild to moderate AD being carried out at 41 sites in

North America. I am an invited reviewer of grants for the National Institutes of Health, the U.S. Alzheimer's Association and its Australian and Canadian counterparts. I also peer review articles pertaining to AD for several major scientific journals. I have been an Alzheimer research consultant to several companies and foundations. In the past year, I consulted for Eisai and Bristol-Meyer Squibb on their Alzheimer research programs. I have presented over 200 invited lectures on AD worldwide, including more than 30 invited lectures on AD immunotherapy.

4. For the past ten years, the primary focus of my research has been characterization of the properties and therapeutic potential of naturally occurring human antibodies against β amyloid. Since 2005, my research has focused specifically on conformation-selective anti-β amyloid auto-antibodies found in human plasma and IGIV. I am familiar with the field and literature of amyloid β conformation generally and conformation specific amyloid β antibodies specifically.

5. A copy of my curriculum vitae is attached as Exhibit A. I am an author of more than 60 peer reviewed articles, including at least 10 articles that involve immunotherapy or anti-amyloid antibodies.

6. I am not a co-inventor of the subject patent application (hereinafter, "the '380 application") and have no financial or business interest in Intellect Neurosciences, Inc., a company that I understand has rights in the '380 application.

7. I have been compensated at my standard consulting rate for my time in studying the materials identified in paragraph 9 and preparing this Declaration.

8. I have been asked to report on whether on April 9, 1997 (i.e., the priority date of the '380 application), a person of ordinary skill in the art would have combined the teachings in Becker et al., European Patent Application No. 0 613 007 ("Becker") and Audia et al., U.S. Patent No. 5,965,614 ("Audia") or Becker, Audia and Johnson-Wood et al., *Proc. Natl. Acad. Sci. USA*, 1997, 94:1550-1555 ("Johnson-Wood") to arrive at the methods set forth in claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 of the '380 application; or would have

combined Becker and Mak et al., *Brain Res.*, 1994, 19:138-142 ("Mak") to arrive at the methods set forth in claims 14, 19, 20, 25, 72, 75, 99-104 and 109-116 of the '380 application.

9. In forming my report, I considered the '380 application, the respective Office Actions that were mailed on May 27, 2009 and November 12, 2009, the references cited in the Office Actions, the respective responses to the Office Actions that were filed by Intellect Neurosciences, the pending claims, the state of the art of antibody therapeutics for Alzheimer's disease as of April 9, 1997, and later-published literature that shed light on the state of the art as of April 9, 1997. I also considered my experience in the field of Alzheimer's research since 1993 and my work with postdoctoral researchers in my lab and AD clinicians in designing and running clinical studies.

10. The subject matter of the '380 application pertains to the art of treating neurodegenerative diseases, particularly as it pertains to treatment of Alzheimer's disease with therapeutic antibodies to amyloid β peptide, particularly "free end-specific" antibodies that bind to amyloid β peptide but do not bind the amyloid precursor protein (APP). Based on my background and experience, one of ordinary skill in this art as of April 9, 1997 would have been a physician with at least 3 years of experience treating patients with therapeutic antibodies and/or treating neurodegenerative diseases generally or a researcher with an M.D. or a Ph.D. in pathology, neurology, psychiatry or related field, with at least 3 years of pre-clinical and/or clinical research experience related to therapeutic antibodies and/or neurodegenerative diseases. In my experience as a clinician and research scientist, I have worked with and supervised physicians and researchers of ordinary skill in the art.

11. Based on my education and experience in the field of treatment of neurodegenerative disorders, I conclude that one of ordinary skill in the art in April 1997 would not have used the 3D6 monoclonal antibody that is described in Audia and Johnson-Wood, or a modification of the polyclonal antibody directed to the C-terminus of amyloid β 1-40 that is described in Mak in the methods of using conformation-specific antibodies that are disclosed in Becker.

12. My reason for arriving at this conclusion is that a person of ordinary skill in the art in April 1997 (such as the post-doctoral research fellows that worked with me in that time frame) would have recognized that Becker's methods explicitly required the use of antibodies selective for specific amyloid β conformations and that the 3D6 monoclonal antibody and modifications of Mak's anti-serum would not have been recognized in April 1997 to have conformational specificity. In view of Becker's clear teaching of the importance of conformational specificity, a person of ordinary skill in the art in April 1997 would not have used the Audia antibody or a modification of the Mak anti-serum in Becker's methods because they would not have believed there was reasonable likelihood that the combined teachings would be successful in treating Alzheimer's disease. The facts that support this conclusion are set out below. Also set out below are errors in the Examiner's interpretation of Becker, Audia, Johnson-Wood and Mak and errors in the Examiner's reasoning that the Examiner appeared to rely upon to reach a conclusion that is contrary to my conclusion.

Becker is Directed Exclusively to Conformation Specific Antibodies to Amyloid β Peptide

13. The vast majority of Becker is directed to antibodies "having a specificity for β-amyloid peptide which is in a predominantly β-sheet conformation." The abstract of Becker, for example, is directed exclusively to such conformation selective antibodies. Becker includes further disclosure concerning antibodies that are selective for the β-sheet conformation of amyloid β protein (Becker at paragraph bridging columns 1 and 2), pharmaceutical formulations of such antibodies (Becker at column 2, lines 5-9), and the use of such antibodies in assays for evaluating the efficacy of agents that inhibit β amyloid peptide neurotoxicity (Becker at column 1, lines 52-56).

14. As noted by the Examiner, Becker also makes mention of conformation specific antibodies that recognize β amyloid peptide in a random coil or α-helix conformation. Becker at column 7, lines 33-38.

15. Becker teaches that β amyloid can be induced to adopt a β-sheet conformation by "aging" peptide in water or tissue culture medium for 1-10 days (Becker at

paragraph bridging columns 2-3; *see* also column 4, lines 31-32) and that "freshly dissolved" β amyloid peptide is "predominantly random coil conformation" (Becker at column 4, lines 30-31).

16. The experimental results reported in Becker relate to showing that there is a direct correlation between β amyloid peptide neurotoxicity and the degree of β-sheet present in the β amyloid peptide. Becker at columns 4-5; *see* column 5, lines 27-30.

17. In view of Becker's careful and repeated reference to conformation specific antibodies and notable lack of reference to antibodies that are not conformation specific, a person of ordinary skill in the art in April 1997 (such as the researchers with whom I worked at the time) would have understood that when Becker refers to "antibodies of the invention" it refers to conformation specific anti-β amyloid peptide antibodies, to the exclusion of anti-β amyloid peptide antibodies that lack conformation specificity. One of ordinary skill in the art would thus have understood that Becker's statement, "The antibodies of the present invention are especially preferred in the diagnosis and/or treatment of Alzheimer's disease," referred in its broadest aspect to conformation specific anti-β amyloid antibodies, and most preferably to antibodies that are specific for β amyloid peptide in the β-sheet conformation.

18. In summary, for the reasons set out in paragraphs 13-17, in April 1997, a person of ordinary skill in the art of the '830 application would have understood that Becker's teachings related to conformation specific anti-β amyloid antibodies and not generally to antibodies that were not conformation specific.

A Person of Ordinary Skill in the Art in April 1997 Would Not Combine Monoclonal Antibody 3D6 With Becker Because the 3D6 Antibody Would Not Have Been Expected to Be a Conformation Specific Antibody and There Was No Reasonable Indication that the 3D6 Antibody Would be an Effective Therapeutic

19. The Johnson-Wood reference teaches that the 3D6 antibody is a mouse monoclonal antibody obtained by immunizing mice with β amyloid peptide amino acids 1-5 conjugated to sheep anti-mouse immunoglobulin. Johnson-Wood at page 1551, column 2,

section entitled "mAb Production." The 3D6 antibody is thus directed to a linear epitope at the amino terminus of Aβ1-40, which is part of the primary structure of the β amyloid peptide.

20. A person of ordinary skill in the art in April 1997, such as the researchers with whom I worked at that time, would have thought it very unlikely that the 3D6 antibody was a conformation specific antibody. Laver et al. (*Cell,* 1990, 61:553-556)[1], for example, teaches that antibodies raised against short peptides, 4-7 amino acids in length (such as 3D6) are in most cases directed against the denatured forms (i.e., epitopes) of a protein, not native conformations. Conversely, in April 1997, a conformation specific antibody would not have been expected to bind to a denatured protein or small protein fragment (as does 3D6). The method used to obtain 3D6 would thus indicate that 3D6 would not have been expected to have conformational specificity. Nor does Audia teach that 3D6 has conformational selectivity. Audia uses the 3D6 antibody as the reporter antibody (for β amyloid peptide amino acids 1-4) in a β-amyloid sandwich ELISA. Audia at column 49, lines 13-17. In April 1997 (and today) a "reporter" antibody would generally be chosen such that it recognizes the total amount of antigen present, i.e., would not be selective only for specific conformations. Likewise, Johnson-Wood makes no mention of 3D6 as being a conformation specific antibody. In summary, based on my experience at the time, a person of ordinary skill in the art in April 1997 would have been highly unlikely to consider the 3D6 antibody to be a member of the class of conformation specific β-amyloid antibodies described in Becker.

21. The principles and properties by which an anti-β amyloid antibody is selected strongly influence its biological effects and side effects. In April 1997, it was known, for example, that in vitro β amyloid disaggregation activity of anti-β amyloid monoclonal antibodies varied greatly, depending on the epitope recognized by an antibody. Solomon et al., *Proc. Natl. Acad. Sci. USA,* 1997, 94:4109-4112. Work in the field of anti-β amyloid immunotherapy over the past decade has confirmed that the therapeutic potential of an antibody is dependent upon the mechanism by which the antibody exerts its effects. *See* Morgan, *J.*

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[1] Counsel has advised me that all of the references I have cited in this Declaration are being submitted in a contemporaneously submitted information disclosure.

Intern. Med., 2011, 269:54-63 (reviewing immunotherapy for Alzheimer's disease and stating at page 57, column 2 that, "different antibodies may utilize different mechanisms to different degrees"). In April 1997, a person of ordinary skill in the art would have understood that there are clear distinctions in the principle Becker described for selecting antibodies (conformation specificity) and the principles used to produce the 3D6 antibody (binding to a short, linear epitope on the N-terminus of β amyloid peptide) and that these respective antibodies are thus substantively different. A person of ordinary skill in the art in April 1997 would have understood that antibodies selected on such different principles would very likely have different therapeutic effects. Likewise, a person of ordinary skill in the art in April 1997 also would have understood that antibodies selected on such different principles may have different side effect profiles. *Id.* ("The extent to which different antibodies utilize different mechanisms may also confer different adverse event profiles for each of the antibodies.") Based on my experience and knowledge of the field, a person of ordinary skill in the art in April 1997 would have recognized these differences as to the potential biological effects and side effects of the respective antibodies to be highly relevant and therefore highly indicative that an antibody such as 3D6 that recognizes a short, linear epitope on the N-terminus of β amyloid peptide should not be substituted for the conformation specific antibody described in Becker.

22. As set out in paragraphs 13-17 above, Becker is directed entirely to antibodies against specific conformations of the β-amyloid peptide. A person of ordinary skill in the art in April 1997 would have understood that Becker sets conformation specificity as a threshold selection criterion for use in Becker's methods and that based on the information available in April 1997, the 3D6 antibody fails to meet this threshold selection criterion. Based on my work in the Alzheimer's disease field at that time, a person of ordinary skill in the art in April 1997 would therefore not have been motivated to use the 3D6 antibody in any method disclosed in Becker.

23. In the Final Office Action that was mailed on November 12, 2009, the Examiner asserts a rationale as to why a person of ordinary skill in the art would use the 3D6

antibody in methods disclosed in Becker. I respectfully disagree with the Examiner's asserted rationale because it is based on certain mistaken facts, assumptions, and/or conclusions.

24. The Examiner's statement that "Becker teaches the administration of any Aβ antibody would be useful to treat Alzheimer's disease" (Final Office Action at page 5, lines 20-21) is not correct. A person of ordinary skill in the art in April 1997 would have recognized that Becker's teachings are unequivocally directed to Aβ antibodies that recognize specific Aβ conformations, with the greatest emphasis placed on the β-sheet conformation. Becker also makes mention of antibodies that recognize Aβ in the α-helical or random coil conformation. In April 1997, almost all anti-β amyloid antibodies were characterized on the basis of their binding to linear epitopes within the primary sequence of the Aβ molecule, not by recognition of specific higher order conformations. Antibody conformational specificity is not synonymous with binding to specific linear sequences of amino acids within Aβ. One of ordinary skill in the art in April 1997 would have recognized that the whole point of Becker was to use such conformation specific antibodies as an alternative to linear epitope, non-conformation specific antibodies. Becker thus does not teach that "any" Aβ antibody can be used to treat Alzheimer's disease. A person of ordinary skill in the art in April 1997 would not have believed that "any" antibody had a reasonable expectation of success for use in treating Alzheimer's disease. To the contrary, in April 1997, a person of ordinary skill in the art would have understood Becker to teach that a limited set of conformation specific antibodies and particularly antibodies specific for the β-sheet conformation, are most useful to treat Alzheimer's disease. Anti-peptide antibodies and specifically, many anti-Aβ antibodies, were known to exist in 1994 when Becker applied for a patent. See, e.g., Saitoh et al., *Sapporo Igaku Zasshi,* 1991, 60:309-20 (English language Abstract included); Bancher et al., *Neurobiol. Aging,* 1989, 10:125-32; Allsop et al., *Proc. Natl. Acad. Sci. USA,* 1988, 85:2790-4; and Kanemaru et al., *Am. J. Pathol.,* 1990, 137:677-87. Becker could have easily indicated that antibodies against linear epitopes were included in the disclosed invention. Becker did not do so, however, and instead focused exclusively on antibodies that recognize higher-order structures of β amyloid peptide. The Examiner's position that Becker teaches "any" Aβ antibody can be used to treat Alzheimer's disease ignores this

important distinction and does not reflect the way that a person of ordinary skill in the art in April 1997 would have interpreted Becker's teachings.

25. The Examiner's assertion that "Becker teaches the administration of any Aβ antibody would be useful to treat Alzheimer's disease" implies that the β-sheet, α-helical and random coil conformations Becker specifies were the full complement of conformations available to the β amyloid peptide. This is not the case. Under certain conditions, proteins or peptides such as β amyloid lose identifiable secondary structure. This is the case when the peptide is in its fully denatured state. *See* commentary by Baldwin et al., *Proc. Natl. Acad. Sci. USA,* 2000, 97:12391-12392. One method for demonstrating that an antibody has conformation specificity is to show that its binding is greatly diminished under conditions that denature its target antigen, such as subjecting the antigen to high temperature or denaturing solvents. Conversely, lack of conformational specificity can be demonstrated by showing that the antibody binds to fully denatured β amyloid that is devoid of higher order structure. Antibodies that bind to denatured β amyloid were known to exist when Becker was filed. Thus, the Examiner's assertion that Becker teaches that all antibodies against β amyloid would be useful to treat Alzheimer's disease is simply wrong, and would have been recognized as being wrong by a person of ordinary skill in the art in April 1997.

26. The official action assumes that if antibodies specific for the random coil or α-helix conformation of β amyloid protein are used in certain of Becker's assays, "the [skilled] artisan would necessarily see that antibodies to the α-helix conformation would prevent neurotoxicity since the β amyloid peptides would be prevented from forming the neurotoxic β-sheet conformation." *See* Final Office Action at page 12, lines 18-21. The official action, however, provides no basis to support the conclusion that an antibody specific for the α-helical conformation would lock β amyloid into that conformation. The binding of a monoclonal antibody to the α-helical conformational epitope may or may not affect the equilibrium between different conformations and could even increase the formation of neurotoxic β-sheet conformations under some circumstances. The assertion that α-helical conformation selective

anti-amyloid antibodies necessarily prevent β-sheet formation was not supported by empiric evidence in April 1997 and remains hypothetical to this day.

27. As it would apply in April 1997, I respectfully disagree with the Examiner's conclusion that:

> The skilled artisan would have been motivated to use the 3D6 antibody, i.e., which is a free-end specific antibody directed to the N-terminus of Aβ, in Becker's therapeutic methods because Audia teaches that said antibody is highly specific for Aβ and does not cross react with other closely related molecules, such as APP.

The Examiner's conclusion, of course, reiterates one of the stated rationales behind the '380 application. *See* '380 application at page 19, lines 23-36 ("It will be readily appreciated by those of skill in the art that the introduction/administration of free end specific molecules will not interfere with the normal biological function of APP or sAPP that are not associated with the formation of Aβ peptides.") Audia, by contrast, uses the 3D6 antibody solely as an in vitro diagnostic for certain forms of Aβ and fails to suggest any benefit of using the 3D6 antibody as a therapeutic. For the reasons set out above, however, as of April 1997, one of ordinary skill in the art would not have been motivated to use the 3D6 antibody in Becker's methods because 3D6 is an amino-terminal free end-specific antibody and is not a conformation specific antibody as taught in Becker. For the reasons set out above, the observation that the 3D6 antibody is an amino terminal free end-specific antibody to β amyloid would not have motivated a person of ordinary skill in the art in April 1997 to use the 3D6 antibody in Becker's conformation-specific treatment methods.

28. The Examiner asserts that one of ordinary skill in the art would have been motivated to use the 3D6 antibody in Becker's methods because Johnson-Wood "teaches that 3D6 binds to amyloid plaques very well" and with "superior ability." *See* Final Office Action at page 17, lines 2-7. Johnson-Wood, however, uses the 3D6 antibody to detect β amyloid in fixed thin sections. The β amyloid in formalin fixed thin sections in Johnson-Wood was chemically

modified and would not necessarily have been expected to retain its native conformations. I was working in the Alzheimer's disease field in April 1997 and I know that at that time it was known to those skilled in the art that the ability of the 3D6 antibody to bind to fixed sections was neither a reasonable predictor of 3D6's therapeutic efficacy in treating Alzheimer's disease nor did it provide evidence that the 3D6 antibody has conformation specificity. The Examiner asserts that Johnson-Wood demonstrates 3D6 binds to amyloid plaques "very well" or with "superior ability." However, Johnson-Wood did not provide a comparison of plaque binding of 3D6 relative to other anti-β amyloid antibodies available at that time. Johnson-Wood failed to provide sufficient experimental details and would not have allowed one of ordinary skill in the art in April 1997 to determine how well it binds to amyloid plaques in vivo. In short, Johnson-Wood failed to provide those skilled in the art in April 1997 a sound rationale for using the 3D6 antibody in Becker's methods.

A Person of Ordinary Skill in the Art in April 1997 Would Not Have Modified and Combined Mak With Becker to Arrive at a Method of Treating Alzheimer's Disease With a Monoclonal Free End-Specific Antibody to the C-Terminal End of β-Amyloid 1-40 Because Such an Antibody Would Not Have Been Expected to Be a Conformation Specific Antibody and There Was No Reasonable Indication that Such An Antibody Would be an Effective Therapeutic

29. Mak disclosed an affinity purified polyclonal antibody that was raised against β amyloid peptide amino acids 34-40 and absorbed against β amyloid peptide amino acids 37-42. Mak at page 138, column 2. The so-called "anti-40" antibody bound Aβ1-40 but did not bind Aβ1-42, when tested on Western blots. *See* Mak, Abstract.

30. A person of ordinary skill in the art in April 1997 would have concluded that Mak's polyclonal antibody was not a conformation-specific antibody because it would recognize multiple epitopes. (Nor is there any indication in Mak that the anti-40 antibody is a

conformation specific antibody.) For the reasons discussed above in connection with the 3D6 antibody, a monoclonal, anti-peptide antibody having the same specificity as the anti-40 antibody would not have been expected by a person of ordinary skill in the art in April 1997 to be a conformation specific antibody.

31. The Examiner asserts that it would have been obvious to make a monoclonal antibody with the same specificity as Mak's anti-40 antibody and use such a monoclonal antibody in Becker's methods, e.g., for treating Alzheimer's disease.

32. The Examiner's assertions are not correct for many of the same reasons stated above in in connection with the rejections based on Becker combined with Audia or Audia and Johnson, including (i) a person of ordinary skill in the art in April 1997 would have understood that Becker's teachings are restricted to conformation specific antibodies; (ii) a person of ordinary skill in the art in April 1997 would have understood the fundamental distinctions between conformation specific antibodies and antibodies targeting linear epitopes; and (iii) Becker does not teach that "any" anti-β amyloid antibody would be useful in Becker's methods. In short, as set out above and based on my experience and knowledge of the field in April 1997, a person of ordinary skill in the art in April 1997 would not have combined Becker and Mak as suggested by the Examiner because such a person would have considered conformational specificity to be a threshold criterion for antibodies to be used in Becker's methods and would not have had a reasonable expectation that the combination could be used successfully to treat Alzheimer's disease.

33. The Examiner misinterprets Mak's teachings about the role of Aβ1-40 in Alzheimer's disease. *See* Final Office Action at page 20, lines 2-5 and page 21, lines 10-11. The passage in Mak relied upon by the Examiner in making his assertions reads:

> Deposition of a 28-43 amino acid peptide, β-protein (Aβ) accompanies Alzheimer's disease (AD). Aβ peptides are normally secreted by cultured cells and found in CSF. Sequencing from cultured cell conditioned medium (CM) and mass spectrographic data from CSF revealed C-terminal heterogeneity with β1-40 (β40) as the major species. In contrast, in isolated amyloid deposits, β1-42

> (β42) appears [as] the major species (85%-95% of plaque core Aβ). Synthetic peptide experiments show that β42 nucleates aggregation of Aβ far better that β39 or β40. In contrast to shorter forms, β42 tends to aggregate, is not readily cleared and accumulates in cells. Collectively, these data argue that the C-terminus of Aβ may be an important variable in AD pathogenesis. To explore this hypothesis, we produced affinity purified polyclonal antibodies to Aβ37-42 which, after β40 column absorption, distinguish β42 from β40.

Mak at page 138, column 1 (citations omitted).

34. A person of ordinary skill in the art in April 1997 would have understood that the above passage from Mak indicates that Aβ42 is a more likely pathogenic agent in Alzheimer's disease than the other forms of Aβ including Aβ40, based on the observations that Aβ42 (i) tends to aggregate and is the highly predominant Aβ species in plaques; (ii) is not readily cleared; and (iii) accumulates in cells. In contrast, a person of ordinary skill in the art in April 1997 would also have understood that this passage indicates that Aβ40 is less likely to be the pathogenic agent of Alzheimer's disease, based on the observations that (i) Aβ40 is a minor component of plaques, notwithstanding that it is "the major" Aβ species in normal CSF; and, as contrasted by Mak with Aβ42, (ii) is more readily cleared; and (iii) is less prone to accumulate in cells.

35. The Examiner's mistaken assertions about Mak's teachings are derived in large part by (i) parsing Mak's disclosure to the extent that it is stripped of its context and meaning and (ii) juxtaposing pieces of information in Mak that are not truly related to each other (e.g., that Aβ1-40 is the major species in normal CSF and the C-terminus of Aβ may be important in Alzheimer's disease). The Examiner thus states that one of ordinary skill in the art would be motivated to use a free end-specific antibody to the C-terminus of Aβ1-40 to treat Alzheimer's disease because, "Mak teaches that this peptide is involved in the neuropathology of Alzheimer's disease, and that this peptide is the major species present in CSF of Alzheimer's disease patients. Further, Mak suggests that the C-terminus of Aβ may be an important variable

in Alzheimer's disease." The Examiner is mistaken to assert that Mak teaches that Aβ1-40 is the major species in the CSF of Alzheimer patients. Seubert et al. (*Nature,* 1992, 359:325-327), the sole reference cited by Mak concerning CSF Aβ1-40, did not study the CSF of Alzheimer's disease patients. To my knowledge, no studies documenting the levels of Aβ1-40 in the CSF of Alzheimer's disease patients had appeared in the medical literature at the time the Mak paper was published. In short, Mak did not (and could not) have taught that Aβ1-40 is the major species present in CSF of Alzheimer's disease patients because this information was not known in 1994 when Mak was filed. The Examiner's assertion that Mak teaches that Aβ1-40 is the major species present in CSF of Alzheimer's disease patients is thus simply wrong.

36. For the reasons set out above in paragraph 34, one of ordinary skill in the art in April 1997 would have understood that Mak teaches that Aβ1-42 is a major component of plaques in Alzheimer's disease whereas Aβ1-40 is the predominant form of Aβ found in normal CSF and is not the predominant Aβ component found in the neuropathology of Alzheimer's disease. Moreover, Tamaoka et al. (*J. Neurol. Sci.,* 1997, 148:41-45) reported no change in the level of Aβ1-40 in the CSF of Alzheimer's disease patients, compared to control groups. This would have further indicated to one of ordinary skill in the art in April 1997 that Aβ1-40 was not the predominant Aβ component in the neuropathology of Alzheimer's disease. In short, the Examiner's statement that Aβ1-40 "is the major species present in CSF of Alzheimer's patients" is misleading in that it suggests the predominance of Aβ1-40 in CSF is specific to Alzheimer's disease when it is not. The Examiner's statement also unfairly characterizes Mak by failing to account for the fact that the properties of Aβ1-40 that were disclosed in Mak would have indicated to a person of ordinary skill in the art in April 1997 that that Aβ1-40 was not a likely pathogenic agent in Alzheimer's disease.

37. Nor does the Examiner's observation that "Mak suggests that the C-terminus of Aβ may be an important variable in Alzheimer's disease pathology" support a conclusion that Aβ1-40 is a pathogenic form of β-amyloid. As evident from the portion of Mak quoted in paragraph 33 above, Mak reviews certain properties of different Aβ species and states,

"*Collectively*, these data argue that the C-terminus of Aβ may be an important variable in AD pathogenesis." As set out in paragraph 33, a person of ordinary skill in the art in April 1997 would understand that the data referred to by Mak *collectively* indicate that Aβ1-42 is the pathogenic agent in Alzheimer's disease and that Aβ1-40 is not likely to be pathogenic. The Examiner's observation that "Mak suggests that the C-terminus of Aβ may be an important variable in Alzheimer's disease pathology" is thus completely stripped of its context. The proper context for this statement is that the C-terminus of Aβ may be an important variable in Alzheimer's disease pathology because Aβ species that vary by only one or two amino acids at their respective C-termini have very different properties, with Aβ1-42 exhibiting pathogenic properties that Aβ1-40 is much less prone to exhibit. When considered in this context, the statement that "Mak suggests that the C-terminus of Aβ may be an important variable in Alzheimer's disease pathology" does not support the Examiner's argument that Mak's teachings would motivate someone of ordinary skill in the art to use a free end-specific antibody to the C-terminus of Aβ1-40 to treat Alzheimer's disease.

Conclusion

38. In summary, for the reasons set forth above, and based on my background and experience in the field of treating Alzheimer's disease, one of ordinary skill in the art in April 1997 would not have used the 3D6 antibody or a monoclonal antibody directed to the C-terminus of amyloid β 1-40 in the methods of using conformation specific antibodies disclosed in Becker because they would understand that Becker's methods required the use of a conformation specific antibody and would not have believed there was a reasonable likelihood that a combining Becker's methods and the 3D6 antibody or a monoclonal antibody directed to the C-terminus of amyloid β 1-40 would have been successful in treating Alzheimer's disease.

39. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the

United States Code, and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Declarant's signature:

/Norman R. Relkin/ January 18, 2011

Norman R. Relkin, M.D., Ph.D. Date

Principal Investigator/Program Director (Last, First, Middle): Relkin, Norman R.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Relkin, Norman R.	POSITION TITLE Associate Professor of Neurology and Neuroscience
eRA COMMONS USER NAME: NRELKIN	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Yale College, New Haven, CT	B.S.	1979	Mol Biophys & Biochem
Yeshiva University, Bronx NY	M.S., Ph.D.	1984, 1987	Neuroscience
Albert Einstein College of Medicine, Bronx, NY	M.D.	1987	Medicine

A. Personal Statement: My research focuses on the characterization of intravenous immunoglobulin (IGIV) as a potential treatment for Alzheimer disease (AD). I have been the Principle Investigator in the Phase 1 and Phase 2 clinical trials of IGIV for AD and I now am leading a pivotal Phase 3 trial of this agent in progress at 41 sites in the U.S. and Canada. These experiences have afforded me a unique opportunity to study the properties of innately occurring human antibodies targeting beta amyloid aggregates that are enriched in IGIV and deficient in persons with AD.

B. Positions and Honors

Positions

1987-1988 Internship, Department of Internal Medicine, New York Hospital-Cornell Medical College
1998-1990 Neurology Resident, New York Hospital-Cornell Medical College
1990-1991 Chief Resident, Department of Neurology, New York Hospital-Cornell Medical College
1991-1992 Fellow in Neurophysiology and Behavioral Neurology, N.Y. Hospital-Cornell Medical College
1992-1997 Assistant Professor of Neurology and Neuroscience, N.Y. Hospital-Cornell Medical College
1992-present Board Certified in Neurology, American Board of Psychiatry and Neurology
1993-present Director, Cornell Memory Disorders Program
1993 -1998 Associate Attending in Neurology, New York Presbyterian Hospital
1997- present Associate Professor of Clinical Neurology & Neuroscience, Weill Cornell Medical College

Appointments and Membership

1990- Member, American Academy of Neurology
1993- Associate Editor, Neurology Alert
1996- Cornell Medical College Committee on Human Rights in Research (IRB)
1999- Executive Committee, Cornell Center on Aging
2000- Professional Advisory Board, Alzheimer's Association, New York Chapter
2001-07 NIH Study Section Member (NAME)
2002-07 Editorial Board, Journal of Clinical Investigation
2009- present Vice Chair, Weill Cornell IRB
2009- present Member, ISTAART
2009- present Editorial Board, Biomarkers in Medicine
2010- present Advisor to the Hydrocephalus Foundation, Eisai, Bristol Meyer Squibb, Pfizer

Awards (selected)

1990 Alpha Omega Alpha Honor Society
1990 Cornell Housestaff Teaching Award
1991 Merle-Smith Fellowship
1991-92 Post doctoral National Research Service Award (NRSA)
1992-97 Lookout Foundation Scholar

2005 Alzheimer's Foundation Distinguished Medical Achievement Award
2001-10 New York Magazine, NY's Best Doctors / Castle Connelly Top Doctors in US

C. Selected peer-reviewed publications (abridged from >60 articles)

1.Jordan BD, Kanik AB, Horwich MS, Sweeney D, Relkin NR, Petito CK, Gandy S. **Apolipoprotein E epsilon 4 and fatal cerebral amyloid angiopathy associated with dementia pugilistica.** *Ann Neurol.* 1995 Oct;38(4):698-9.

2. Relkin NR, Kwon YJ, Tsai J, Gandy S. **The National Institute on Aging/Alzheimer's Association recommendations on the application of apolipoprotein E genotyping to Alzheimer's disease.** *Ann N Y Acad Sci.* 1996 Dec 16;802:149-76.

3. Gouras GK, Relkin NR, Sweeney D, Munoz DG, Mackenzie IR, Gandy S. **Increased apolipoprotein E epsilon 4 in epilepsy with senile plaques.** *Ann Neurol.* 1997 Mar;41(3):402-4.

4. Post SG, Whitehouse PJ, Binstock RH, Bird TD, Eckert SK, Farrer LA, Fleck LM, Gaines AD, Juengst ET, Karlinsky H, Miles S, Murray TH, Quaid KA, Relkin NR, Roses AD, St George-Hyslop PH, Sachs GA, Steinbock B, Truschke EF, Zinn AB. **The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective.** *JAMA.* 1997 Mar 12;277(10):832-6.

5. Kwok JB, Taddei K, Hallupp M, Fisher C, Brooks WS, Broe GA, Hardy J, Fulham MJ, Nicholson GA, Stell R, St George Hyslop PH, Fraser PE, Kakulas B, Clarnette R, Relkin N, Gandy SE, Schofield PR, Martins RN. **Two novel (M233T and R278T) presenilin-1 mutations in early-onset Alzheimer's disease pedigrees and preliminary evidence for association of presenilin-1 mutations with a novel phenotype.** *Neuroreport.* 1997 Apr 14;8(6):1537-42.

6. Jordan BD, Relkin NR, Ravdin LD, Jacobs AR, Bennett A, Gandy S. **Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing.** *JAMA.* 1997 Jul 9;278(2):136-40.

7. Xu H, Gouras GK, Greenfield JP, Vincent B, Naslund J, Mazzarelli L, Fried G, Jovanovic JN, Seeger M, Relkin NR, Liao F, Checler F, Buxbaum JD, Chait BT, Thinakaran G, Sisodia SS, Wang R, Greengard P, Gandy S. **Estrogen reduces neuronal generation of Alzheimer beta-amyloid peptides.** *Nat Med.* 1998 Apr 1;4(4):447-51.

8. Gouras GK, Xu H, Jovanovic JN, Buxbaum JD, Wang R, Greengard P, Relkin NR, Gandy S. **Generation and regulation of beta-amyloid peptide variants by neurons.** *J Neurochem.* 1998 Nov;71(5):1920-5.

9. Sheu KF, Brown AM, Haroutunian V, Kristal BS, Thaler H, Lesser M, Kalaria RN, Relkin NR, Mohs RC, Lilius L, Lannfelt L, Blass JP. **Modulation by DLST of the genetic risk of Alzheimer's disease in a very elderly population.** *Ann Neurol.* 1999 Jan;45(1):48-53.

10. Gouras GK, Tsai J, Naslund J, Vincent B, Edgar M, Checler F, Greenfield JP, Haroutunian V, Buxbaum JD, Xu H, Greengard P, Relkin NR. **Intraneuronal Abeta42 accumulation in human brain.** *Am J Pathol.* 2000 Jan;156(1):15-20.

11. Kutner KC, Erlanger DM, Tsai J, Jordan B, Relkin NR. **Lower cognitive performance of older football players possessing apolipoprotein E epsilon4.** *Neurosurgery.* 2000 Sep;47(3):651-7;

12. Relkin N. **Screening and early diagnosis of dementia.** *Am J Manag Care.* 2000 Dec;6(22 Suppl):S1111-8; discussion S1119-24.

13. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, Small GW, Miller B, Stevens JC. **Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology.** *Neurology.* 2001 May 8;56(9):1143-53.

14. Taddei K, Fisher C, Laws SM, Martins G, Paton A, Clarnette RM, Chung C, Brooks WS, Hallmayer J, Miklossy J, Relkin N, St George-Hyslop PH, Gandy SE, Martins RN. **Association between presenilin-1 Glu318Gly mutation and familial Alzheimer's disease in the Australian population.** *Mol Psychiatry.* 2002;7(7):776-81.

15. Weksler ME, Relkin N, Turkenich R, LaRusse S, Zhou L, Szabo P. **Patients with Alzheimer disease have lower levels of serum anti-amyloid peptide antibodies than healthy elderly individuals.** *Exp Gerontol.* 2002 Jul;37(7):943-8.

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18. Relkin NR, Reichman WE, Orazem J, McRae T. **A large, community-based, open-label trial of donepezil in the treatment of Alzheimer's disease.** *Dement Geriatr Cogn Disord.* 2003;16(1):15-24.

19. Roberts JS, LaRusse SA, Katzen H, Whitehouse PJ, Barber M, Post SG, Relkin N, Quaid K, Pietrzak RH, Cupples LA, Farrer LA, Brown T, Green RC. **Reasons for seeking genetic susceptibility testing among first-degree relatives of people with Alzheimer disease.** *Alzheimer Dis Assoc Disord.* 2003 Apr-Jun;17(2):86-93.

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21. Cupples LA, Farrer LA, Sadovnick AD, Relkin N, Whitehouse P, Green RC. **Estimating risk curves for first-degree relatives of patients with Alzheimer's disease: the REVEAL study.** *Genet Med.* 2004 Jul-Aug;6(4):192-6.

22. Roberts JS, Barber M, Brown TM, Cupples LA, Farrer LA, LaRusse SA, Post SG, Quaid KA, Ravdin LD, Relkin NR, Sadovnick AD, Whitehouse PJ, Woodard JL, Green RC. **Who seeks genetic susceptibility testing for Alzheimer's disease? Findings from a multisite, randomized clinical trial.** *Genet Med.* 2004 Jul-Aug;6(4):197-203.

23. LaRusse S, Roberts JS, Marteau TM, Katzen H, Linnenbringer EL, Barber M, Whitehouse P, Quaid K, Brown T, Green RC, Relkin NR. **Genetic susceptibility testing versus family history-based risk assessment: Impact on perceived risk of Alzheimer disease.** *Genet Med.* 2005 Jan;7(1):48-53.

24. Weksler ME, Gouras G, Relkin NR, Szabo P. **The immune system, amyloid-beta peptide, and Alzheimer's disease.** *Immunol Rev.* 2005 Jun 1;205:244-56.

25. D'Ascenzo M, Relkin NR, Lee KH. **Alzheimer's disease cerebrospinal fluid biomarker discovery: a proteomics approach.** *Curr Opin Mol Ther.* 2005 Dec;7(6):557-64.

26. Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Green RC, REVEAL (Risk Evaluation and Education for Alzheimer's Disease) Study Group. **Genetic risk assessment for adult children of people with Alzheimer's disease: the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study.** *J Geriatr Psychiatry Neurol.* 2005 Dec;18(4):250-5.

27. Relkin N. **Are cholinesterase inhibitors more than symptomatic treatments for Alzheimer disease?** *Alzheimer Dis Assoc Disord.* 2006 Apr-Jun;20(2 Suppl 1):S2.

28. Reilly MC, Relkin NR, Zbrozek AS. **Development and testing of a new outcome measure of relationship between patients with Alzheimer's disease and their partners.** *Am J Alzheimers Dis Other Demen.* 2006 Aug-Sep;21(4):249-57.

29. Eckert SL, Katzen H, Roberts JS, Barber M, Ravdin LD, Relkin NR, Whitehouse PJ, Green RC. **Recall of disclosed apolipoprotein E genotype and lifetime risk estimate for Alzheimer's disease: the REVEAL Study.** *Genet Med.* 2006 Dec 1;8(12):746-51.

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33. Relkin NR. **Beyond symptomatic therapy: a re-examination of acetylcholinesterase inhibitors in Alzheimer's disease.** *Expert Rev Neurother.* 2007 Jun;7(6):735-48.

34. Choe L, D'Ascenzo M, Relkin NR, Pappin D, Ross P, Williamson B, Guertin S, Pribil P, Lee KH. **8-plex quantitation of changes in cerebrospinal fluid protein expression in subjects undergoing intravenous immunoglobulin treatment for Alzheimer's disease.** *Proteomics.* 2007 Oct;7(20):3651-60.

35. Sabbagh MN, Richardson S, Relkin N. **Disease-modifying approaches to Alzheimer's disease: challenges and opportunities-Lessons from donepezil therapy.** *Alzheimers Dement.* 2008 Jan;4(1 Suppl 1):S109-18.

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41. Relkin NR, Szabo P, Adamiak B, Burgut T, Monthe C, Lent RW, Younkin S, Younkin L, Schiff R, Weksler ME. **18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease.** *Neurobiol Aging.* 2009 Nov;30(11):1728-36.

42. Hughes RA, Dalakas MC, Cornblath DR, Latov N, Weksler ME, Relkin N. **Clinical applications of intravenous immunoglobulins in neurology.** *Clin Exp Immunol.* 2009 Dec;158 Suppl 1:34-42

43. Szabo P, Mujalli DM, Rotondi ML, Sharma R, Weber A, Schwarz HP, Weksler ME, Relkin N. **Measurement of anti-beta amyloid antibodies in human blood.** *J Neuroimmunol.* 2010

D. Other Support

1. NIH U01 AG01483 **Aisen/Relkin (Project Director)** **4/2007-6/30/2011**
Alzheimer's Disease Cooperative Study (ADCS) / Project: Intravenous Immunoglobulin (IVIg) for Treatment of Alzheimer's disease
The primary aim of this 40 site multicenter clinical trial is to determine whether IVIg treatment for 18 months slows the rate of decline of dementia symptoms in patients with mild to moderate Alzheimer's disease.

2. K23 NS045051 **Katzen (PI)/Relkin (Mentor)** **5/10/06-5/08/11**
Recovery of Cognitive Functions Following Shunt Placement in Normal Pressure Hydrocephalus
The major goal of this project is to examine cognitive outcome in NPH following placement of programmable shunts. A second goal is to determine whether shunting parameters contribute to cognitive outcome in NPH.

3. Baxter Healthcare/WCMC GCRC **Relkin (PI)** **12/2006-12/2010**
A Randomized Double-Blind Placebo-controlled Phase II study of Intravenous Immunoglobulin (IVIg) for treatment of Mild-Moderate Alzheimer's disease (AD)
The overall goal of this Phase II study is to evaluate the safety, efficacy and biological effects of IVIg in the treatment of Alzheimer's disease (AD). This study is in open label extension.

4. Baxter Healthcare/WCMC GCRC **Weksler/Relkin (co-PI)** **12/2004-12/2010**
Phase I study of IVIg for treatment of Mild-Moderate Alzheimer's disease (AD)
The overall goal of this Phase I study is to evaluate biological effects of IVIg in patients with Alzheimer's disease (AD). This study is in open label extension.

5. Leonard Levy Foundation **Relkin (PI)** **10/2007-10/2010**
Improved characterization of NPH
This study employs proteomics technology and quantitative diffusion tensor imaging in service of improving diagnosis and prognostication in cases of NPH.

6. Hydrocephalus Association **Moore(PI)/Relkin (Mentor)** **1/2010-1/2012**
Volumetric studies of the Brain in NPH
This study uses volumetric analysis of MRI data to improve diagnosis of NPH